IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Appl. No.	: 10/731,465	Confirmation No. 5274
Applicants	: Whitsett, *et al*	
Filed	: December 9, 2003	
Title	: METHODS OF DIAGNOSIS AND TREATMENT OF INTERSTITIAL LUNG DISEASE	
TC/A.U.	: 1632	
Examiner	: Montanari, David A.	
	:	
Docket No.	: 0010872.0507287	
Customer No.	: 26874	

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This declaration under 37 CFR Sec. 1.132 is supportive of the Amendment and Response filed herewith. I, Jeffrey A. Whitsett, declare and say:

1. That I am a citizen of the United States and that I am one of the co-inventors in the above-referenced patent application; that I am employed by Cincinnati Children's Medical Center, and I was and still am, engaged in a research program in the field of Neonatology, Perinatal and Pulmonary Biology;

2. That I am familiar with the above-identified patent application Ser. No. 10/731,465, that I have reviewed the July 14, 2006 Office Action in the above captioned case; and that I am familiar with the following reference: U.S. Patent 6,838,428 B2 (Whitsett);

3. That the inventorship of the current application is correct and that any invention disclosed but not claimed in the Whitsett reference cited by the Examiner was invented by both myself and Stephen Glasser as co-inventors and not solely invented by the listed inventor of the publication notwithstanding the inventorship of the patent and is thus not an invention by another;

4. That in the July 14, 2006 Office Action in the above captioned case, I am familiar with the several reviews, *e.g.*, Brown (2005, *Expert Opinion Drug Delivery*, Vol. 2(1), pgs. 29-42), and I contend that the in the rejection based upon the alleged unpredictability in "protein therapy" and recombinant SP-C, the examiner misunderstands the therapy with either SP-C or SP-D. Neither therapy is intended to deliver proteins systemically, but to deliver them to the surface of the airways and alveoli. Aerosol or instillation therapy for a variety of disorders is standard in clinical practice. Numerous drugs have been delivered to the airway epithelium (*e.g.* glucocorticoids for treatment of asthma and surfactant therapy for acute respiratory distress syndrome). In the latter, protein-lipid mixtures are administered to the lung, where the effects of the drug are local. The surfactant proteins function in the airways and in the surface epithelium, and can be readily delivered for therapy of lung disease. Provided are several references demonstrating the feasibility of this therapy with SP-D and SP-B for acute diseases as tested in mice or sheep (1-3). Therapy with SP-B, SP-C, and SP-D has been highly effective in rodent and sheep models of acute lung disease, and there is no reason to expect that they cannot be delivered chronically by aerosol or instillation. There is no evidence that SP-C has systemic functions outside the lung at present. Treatment for SP-C abnormalities is intended to be local.

5. That the references enclosed herein use both recombinant SP-C-like peptides, recombinant SP-D, and purified SP-B as examples for therapy of acute lung disorders. Patients with mutations in the SP-C gene generally do not produce the active peptide (SP- C) needed in the airway. Even when the mutation is heterozygous, processing of the normal preproprotein (proSP-C) to active SP-C is inhibited by the mutant protein. Thus, replacement of the SP-C peptide to the lung represents a potential therapy. We have shown that deficiency of SP-C per se also causes severe lung disease in the knockout mice and have identified human patients that lack expression of both proSP-C and SP-C; therefore replacement of SP-C represents a potential therapy for this rare subset of patients when given into the lung. Finally, clinical mutations in which proSP-C is misprocessed or its synthesis is inhibited secondarily, as in severe lung injury, will have a decreased SP-C that can be replaced by delivery of the recombinant protein to the lung. We have also shown that in conditions in which a surfactant protein is deficient, but not absent, additional surfactant protein can prevent further lung injury (*e.g.* as shown in Hokuto et al., Stat-3 is required for pulmonary homeostasis during hyperoxia. J. Clin. Invest. 113:28-37, 2004).

6. That to make use of the invention, one would produce a formulation of the surfactant protein, recombinant SP-C or SP-C-like peptide, with or without lipid carriers, for example and without limiting ourselves in any way, mixed 1-5% by weight with phosphytidalcholine (30-50 mg/kg), suspended in normal saline or buffered saline and given intratracheally or by aerosol. The protein-lipid mixture can be administered by aerosol or instillation to the airway surface. Since the half-life of surfactant components, including lipids and proteins is 6-12 hours in the mature lung, therapy could be repeated Q12h to daily. Such preparations are utilized routinely for the surfactant therapy of acute respiratory distress syndrome in premature infants. These infants have been successfully treated for many years in clinical practice. References given are standard for delivery of protein to the lung, and are not intended for systemic delivery of the peptide. Surfactant therapy for acute lung disease (RDS) in preterm infants, providing a lipid or lipid-protein mixture to the lung has been a standard therapy for RDS in preterm infants for more than 25 years (see Whitsett, J.A.:

Pulmonary surfactant and respiratory distress syndrome in the newborn infant. In: The Lung: Scientific Foundations, 2nd Edition, R.G. Crystal, J.B. West, E.R. Weibel and P.J. Barnes (eds.). Raven Press, New York, NY, Chapter 165:2167-2177, 1996).

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not.

Jeffrey A. Whitsett

Dr. Jeffrey A. Whitsett

1/09/07

Date

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